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# General Discussion





The aim of this thesis was to investigate the patient, procedural, and device-related factors that affect clinical outcomes in transcatheter aortic valve implantation (TAVI). In this chapter, the results of this body of research will be considered and contextualized to current clinical practice. Future developments in the field of transcatheter heart valves (THV) will be considered.

## INTRODUCTION

Transcatheter aortic valve intervention has evolved greatly since Professor Alain Cribier performed the first balloon aortic valvuloplasty to treat severe aortic stenosis in 1986.<sup>1</sup> While the impressive acute hemodynamic result achieved with balloon valvuloplasty were diminished by valve restenosis and symptoms recurred within 6–8 months,<sup>2</sup> Cribier had demonstrated that transcatheter valvular intervention was feasible. Perhaps technique refinement could produce an effective durable treatment for the 30–60% of patients who are refused surgery?<sup>3</sup>

In 2002, some 15 years after the first balloon valvuloplasty, Cribier implanted a first generation 23mm bovine pericardial stent valve developed by Percutaneous Valve Technologies (Fort Lee, NJ).<sup>4</sup> The recipient was a 57-year-old man with refractory cardiogenic shock secondary to severe aortic stenosis, who was denied traditional aortic valve surgery. The intervening decade has seen dramatic developments in transcatheter valve technology, and a wealth of knowledge has been acquired with respect to patient selection, procedural techniques, and post-procedure care. These refinements have greatly improved patient safety and procedural outcomes, and TAVI is now considered to be the standard of care for patients at high or excessive risk for conventional surgical aortic valve replacement.<sup>5-7</sup>

Patient selection can be especially challenging for complex procedures such as TAVI, where the patient's expectations, the clinical situation, co-morbid medical conditions, peripheral and aortic vascular anatomy require careful consideration. In **Chapter 2**, we provide a comprehensive description of the anatomy of the aortic valvar complex from the point of view of the TAVI physician. This chapter is derived from an interactive iPad application specifically created to serve as a reference tool for institutional TAVI teams. This application provides a comprehensive visual interactive and dynamic tool for TAVI operators of all levels, and features in excess of 800 videos and figures. The anatomy chapter is illustrated with high quality images, detailed figure legends, and interactive videos with anatomist Professor Robert Anderson.

Careful, considered patient selection by a team of experienced interventional cardiologists, cardiac surgeons, anaesthetists, and imaging specialists (the institutional heart team) has been at the core of the TAVI success story (**Chapter 3**). Surgical risk has been quantified using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), EuroSCORE II, and the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality score. However, these scores share important limitations in high-risk patient subsets, most notably

a limited predictive capacity and an inability to capture significant comorbid conditions in what is a heterogeneous patient group. The logistic EuroSCORE for example, has a low discriminatory power in TAVI patients (C statistics 0.61 to 0.64). As such, TAVI has fostered a new era of cooperation between a variety of hospital-based services, including cardiologists, cardiac surgeons, anaesthetists, elderly-medicine physicians, imaging specialists, and allied health professionals. Together, the institutional heart team can draw on a much greater pool of experience to determine (A) if TAVI is the most appropriate option for the patient, (B) if the anatomy is suitable, and (C) identify the optimal procedural technique.

Careful pre-operative multimodal imaging assessment is fundamental for optimizing TAVI outcomes (**Chapter 5**). Pre-procedural anatomical screening is of considerable importance for TAVI. In particular, appropriate THV sizing is recognized to be a key factor for optimizing patient outcomes: PVL is an independent risk factor for mortality and has been reported in 9% to 21% of CoreValve and 6% to 13.9% of Edwards SAPIEN recipients.<sup>8,9</sup> Appropriate THV sizing involves achieving a predefined amount of prosthesis oversizing relative to the aortic annulus. Previous studies have demonstrated that failing to achieve a 1:1 ratio of the THV relative to the aortic annulus (cover index:  $[\text{TAVR area}/\text{annular area} - 1] \times 100$ ) is associated with PVL.<sup>10</sup> CT provides more accurate annular measurements than TOE does, and the use of CT for THV sizing has been associated with improved clinical outcomes.<sup>10</sup> CT multiplanar reformatting allows accurate 3D reconstruction of the aortic annulus in its true plane. The superiority of this technique over 2D TOE is explained by the oval shape and variable orientation of the aortic annulus and the likelihood that 2D echocardiographic imaging will measure a short-axis tangent across the annulus. In **Chapter 5**, we confirmed that previous observations that CT-based aortic annular diameters are significantly larger than those obtained by 2D echocardiography. When these CT diameters were used to recalculate the oversizing relative to the TOE-selected CoreValve, the actual THV oversizing was reduced by 50%. Accordingly, the retrospective CT analysis suggested that up to 50% of patients did not achieve the manufacturer's recommended THV-oversizing criteria and therefore received an inappropriate CoreValve size. CT data also suggested that one-third of patients had annuli too large for available CoreValve sizes during the time of enrolment. Adherence to CT-based but not TOE-based oversizing was a predictor of reduced PVL. According to CT, significantly lower PVL rates were observed in those patients who received a correct CoreValve size than in those who did not. These data, combined with other studies, have resulted in MSCT being considered as the gold standard technique for THV-size determination.

## PART II. TAVI CANDIDATES AND TECHNOLOGY ADOPTION

### TAVI Candidates

There remain few studies reporting the prevalence of valvular heart disease, and in particular, aortic stenosis in the general population. We undertook a systematic review and meta-analysis on the prevalence of aortic stenosis in the elderly ( $\geq 75$  years), and estimated a prevalence rate of 3.4% (**Chapter 6**). Using pooled estimates from studies reporting clinical decision-making in severe aortic stenosis, we projected the number of TAVI candidates in Europe and North America. In agreement with the Euro Heart Survey,<sup>11</sup> we found that up to 40.5% of all elderly patients with severe symptomatic aortic stenosis do not undergo surgical aortic valve replacement. While there were differences between studies, specifically related to the time period and the reporting of aortic stenosis severity and symptoms, this analysis was the first to assess these parameters across studies, and confirms the undertreatment of aortic stenosis in elderly patients.<sup>3</sup>

Using the clinical decision-making algorithm, we estimate that there are 190,000 TAVI candidates in Europe, and 100,000 in the United States. Furthermore, we calculated that there are 27,000 new TAVI candidates between these regions per annum. The heterogeneity of the underpinning studies yielded wide confidence intervals for these figures, and therefore they should be considered as estimates, however this study is the first to provide some guidance as to the potential of the TAVI market in Europe and North America.

### TAVI Adoption

Disparate adoption of medical technology is pervasive and usually results in inequitable patient access. Regional differences in TAVI adoption are likely to have emerged because of variations in social, regulatory, economic, and political circumstances, as well as disease prevalence and longevity. However, the adoption kinetics of a novel medical technology such as TAVI and the factors influencing these variables have not been previously described. We investigated TAVI utilization in 11 Western European Nations and found significant variability in the use of TAVI among nations (**Chapter 7**): in 2011, the number of TAVI implants per million individuals ranged from 6.1 in Portugal to 88.7 in Germany ( $33 \pm 25$ ). Furthermore, we linked TAVI use to a number of national financial indices and healthcare parameters and found that two factors were strongly associated with TAVI adoption: national healthcare spending per capita correlated with TAVI use ( $r = 0.80$ ;  $p = 0.005$ ); and the presence of TAVI-specific reimbursement (as apposed to TAVI reimbursement from general hospital budget) was associated with greater TAVI implant rates ( $698 \pm 232$  vs.  $213 \pm 112$  implants/million individuals  $\geq 75$  years;  $p = 0.002$ ). When we applied the implant numbers to the estimated number of TAVI candidates identified in our earlier study, we found that TAVI penetration ( $[\text{actual use} / \text{potential use}] \times 100$ ) across Europe was low (17.9%). Penetration rates ranged from 3.4% in Portugal to 36.2% in Germany.

Overall, these data suggest that TAVI is underutilized in Western Europe, particular in less affluent nations without specific reimbursement for THVs. Such disparity is axiomatic, and has been previously demonstrated for a variety of high-tech medical therapies.<sup>12</sup> The identification of such inequitable access to medical technologies is important because it generates discussion and initiatives to address inequalities and the corresponding impact on patient outcomes through payer- and physician-led programs. It is therefore encouraging to see the recently announced introduction of the Valve-For-Life program by the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Similar to the stent-for-life initiative, this program aims to improve the delivery of care and patient access to TAVI, thereby reducing mortality and morbidity in patients suffering with valvular heart disease.<sup>13</sup>

The process of approval for THVs is also an important subject considered in this thesis. In Europe, THVs and surgical prostheses share a common market approval process: the Conformité Européenne (CE) mark provides authorization for a manufacturer to sell a product in the European Economic Area by affirming that it complies with pre-specified legal requirements. Importantly, the level of scientific evidence required to achieve CE-mark requires a single-arm demonstration of short-term safety and efficacy in approximately 50 patients. In contrast, the approval process for new-generation surgical or transcatheter prostheses in the US is very different. For surgical prostheses, the development of objective performance criteria (OPC) by the Food and Drug Administration (FDA) has superseded the requirement to perform RCTs due to the maturity of the device field and the minimal changes in new iterations of previously approved valves (predicate devices). Up until recently, approval of THVs has required randomized comparisons to standard FDA-approved therapies since the technology is immature, device design significantly different and device development still iterating rapidly. However, similar to the development of surgical prostheses, the established efficacy of TAVI as shown in multiple RCTs of high-risk patients has potentially made the requirement for lengthy RCTs before introducing new THV devices unacceptable from a societal, patient and physician standpoint. It may place patients at unnecessary risk by delaying access to improved safer and more efficient technology. Therefore, alternative study approaches should be considered for new THV-device approval.

The FDA recently also approved several THVs based on single-arm studies, the first one being the CoreValve device that was tested in the CoreValve Extreme Risk Pivotal trial. Innovative trial designs, perhaps incorporating OPC, have been proposed but not formally introduced as alternatives to RCTs for new THV-device approval. **Chapter 8** provides an overview of OPC, considers the potential role of OPC for THV-device approval, and discusses the challenges associated with such an approach. Several recommendations for the future implementation of OPC for THV devices are provided.

### PART III. NOVEL APPLICATIONS OF TAVI TECHNOLOGY

Transcatheter heart valve technology has already expanded well beyond the initial focus of Professor Cribier's endeavours. TAVI is now frequently applied to a variety of off-label clinical situations, including intermediate / low risk patients, bicuspid aortic valve morphology, and the development of alternate vascular access routes. Perhaps the most notable adaptation of this technology is the treatment of patients with failing surgical bioprosthetic valves (**Chapters 9, 10, 11, 12**). In 2007, Wenaweser and colleagues reported the implantation of a Medtronic CoreValve (Medtronic CV, Luxembourg S.a.r.l.) into a degenerated surgical aortic bioprosthesis.<sup>14</sup> Since this first case, numerous transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) procedures have been performed and experienced physicians are adapting current THVs for treatment of failing surgical atrioventricular and pulmonary bioprostheses. Optimal results for valve-in-valve or valve-in-ring procedures require a thorough knowledge of surgical bioprosthesis construction or ring morphology. In these chapters, we provide detailed descriptions of the construction of surgical bioprostheses and their failure modes and outline the importance of pre-procedural imaging for TAV-in-SAV procedures. Furthermore, we provide a comprehensive step-by-step guide for THV sizing and procedural planning for TAVI practitioners undertaking these procedures. As for the anatomy section described above, **Chapter 11** is derived from the interactive TAVI Atlas that provides the clinician with a high-quality and interactive guide to TAV-in-SAV procedures. Numerous videos are included in this iPad application demonstrating the specific implantation technique required for each TAV-in-SAV procedure.

As it is unlikely that a randomized trial will be conducted to formally compare redo surgery and TAV-in-SAV treatment strategies, we conducted a propensity-matched analysis comparing these treatments (**Chapter 12**). We found that 30-day and 1-year mortality, stroke, and a host of other hard endpoints were comparable between groups. Hospital stay was however shorter in the TAV-in-SAV cohort. Thus, current data support the treatment of patients with failing surgical bioprostheses at high operative risk using THV technology in specialised centres. Longer-term data is of course required to validate this approach, particularly in younger patients, but it is possible that these innovative procedures will become the standard of care for surgical bioprosthetic valve dysfunction.<sup>15</sup>

Bicuspid aortic valve (BAV) is a heritable disease affecting 0.5% to 2% of the general population, with a strong male predilection. BAV stenosis and/or regurgitation is the most common indication for SAVR in patients <70 years of age. BAV morphology was excluded from the landmark TAVI trials involving as abnormal cusp fusion, pronounced asymmetry of the valve orifice and annulus, heavily calcified and fibrotic leaflets, and calcified raphe could adversely affect the expansion of transcatheter valves and lead to paravalvular aortic regurgitation and poor haemodynamic function. We therefore undertook a multicenter study to assess the safety and efficacy of TAVI in BAV in a large group of patients, and to assess hae-

modynamic, echocardiographic, and clinical outcomes (**Chapter 13**).<sup>16</sup> We studied 139 elderly patients with BAV undergoing TAVI across 12 European and Canadian centres. We found that the application of TAVI to BAV morphology was associated with similar clinical outcomes to patients with tricuspid aortic valve stenosis, though with  $\geq$ grade 2 post-implantation paravalvular leak in 28% of cases at 30-days. Underscoring the importance of MSCT-based valve sizing in these patients, this figure fell to 17.4% in among patients undergoing MSCT-sizing. Nevertheless, this study demonstrated for the first time that results of TAVI were suboptimal in patients with BAV morphology, and thus that it should be used reservedly. There is the potential for novel THV devices that are repositionable and/or have sealing cuffs to mitigate the higher rates of PVL. Nevertheless, it is important to state that in patients with BAV disease, SAVR should continue to be considered the first line therapy, unless patients are considered by the institutional heart team to be at high-surgical risk or indeed inoperable. As TAVI expands into lower risk populations, the question of equivalent efficacy to SAVR in patients with BAV will become more acute, as BAV is highly represented in these younger cohorts. Physicians, medical societies, the medical device industry, and other stakeholders have a responsibility to ensure TAVI technology is appropriately tested in randomized controlled trials in such patients.

Transcatheter valve technology is evolving rapidly. New-generation devices require smaller vascular access sheaths for valve delivery, are recapturable and repositionable and have sealing skirts to reduce paravalvular leak, and deflectable delivery catheters allowing the operator to attempt more challenging anatomy. The Medtronic Evolut R with in-line sheath technology is a novel THV device described within these pages (**Chapter 14**). We reported the first human case using this recapturable, repositionable, retrievable device in a patient with a severely stenotic failing aortic bioprosthesis.<sup>17</sup> This newly designed delivery catheter is a 14 Fr-equivalent system. Given that major vascular complications are associated with considerable morbidity and mortality, and that the ratio of the outer diameter of the delivery sheath to the femoral artery (SFAR) is a strong predictor of these complications,<sup>18</sup> the 4 Fr reduction in sheath size compared to the system predecessor is likely to extend the potential and safety of transfemoral TAVI. Applying the SFAR ratio to the EnVeo R system, transfemoral TAVI can be safely performed in patients with iliofemoral diameters as small as 5.4mm. Indeed, if the 20% oversizing ratio between the introducer sheath (18 Fr: outer diameter 7.2 mm) and the minimal femoral artery diameter (6 mm) is maintained, then femoral anatomy as small as 5 mm could be navigated with the EnVeo R delivery catheter. Such advancements are of course related to the ever-decreasing morbidity and mortality associated with TAVI.

Despite the reduction in the size of the vascular sheaths required for TAVI, transfemoral procedures are challenging or impossible in up to one-quarter of TAVI candidates. In such cases, a variety of alternate vascular access routes have been described: transapical, transaxillary, direct aortic, and transcaval. Each of these alternative strategies may be undesirable in certain clinical and anatomical situations, and each may be associated with adverse clinical



consequences, including greater invasiveness, post-procedural pain, delayed mobility and patient discharge, and perhaps, increased mortality in the case of the transapical route. Herein, we described the largest series of patients undergoing TAVI using a transcarotid vascular access route (**Chapter 15**).<sup>19</sup> Among 96 patients treated at 3 French sites, successful vascular access was achieved in all cases, without any access site vascular complications. The 30-day and 1-year mortality rates were 6.3 and 16.7%, respectively, and procedural success and efficacy were similar to other alternate vascular access series. Stroke was an endpoint of particular importance, as high rates of cerebrovascular complications could significantly limit the application of the technique. Gratifyingly, at 30-days we observed no stroke and only 6 TIA. It is interesting to note that many of these TIA events were contralateral to the carotid vascular access site. Thus, there may be several potential stroke mechanisms during transcarotid TAVI: 1) embolization of carotid artery plaque due to arterial puncture and instrumentation; 2) access site trauma providing a nidus for thrombosis with subsequent embolization; 3) inadequate collateral perfusion through the circle of Willis; and 4) embolization of debris during balloon valvuloplasty or THV implantation. The low rate of stroke observed in this study may be attributed to careful patient selection (common carotid artery minimal lumen diameter >7.0 mm), mandatory pre-treatment with dual antiplatelet agents, and adequate intraoperative anticoagulation (activated clotting time >250 s). We also limited the duration of antegrade ischaemia by placing the large bore introducer sheath only when necessary. Nevertheless, there remains the potential to further reduce the risk of cerebral ischaemia by limiting THV postdilatation, using embolic protection devices, and by further refining the anatomical selection criteria for transcarotid TAVI. These data support the feasibility of transcarotid arterial access for TAVI and encouraging short- and medium-term clinical outcomes.

## PART IV. TRANSCATHETER HEART VALVE FAILURE

Ever-improving procedural safety and promising medium-term clinical efficacy have encouraged the application of THV technology to lower risk patients. Indeed, two randomized trials of TAVI in intermediate-risk patients are expected to report in the next year, and the US FDA has granted permission for randomized TAVI trials in low-risk patients. In this context, understanding the modes of THV failure and exploring valve durability and long-term clinical efficacy are of vital importance (**Chapter 16**). A variety of failure modes have been described for surgical bioprostheses, including infective endocarditis (IE), thrombosis, and structural valve failure (SVF). Surgical bioprosthetic failure has been clearly described and quantified, while in contrast, a systematic description of THV failure has not been performed. We performed a systemic review of all published cases of THV failure to address this knowledge gap.<sup>20</sup> Among 70 publications, we identified 87 individual cases of THV failure. Similar to surgical bioprosthetic heart valve failure, we observed cases of prosthetic valve endocarditis (PVE),

structural valve failure, and THV thrombosis. The microbiological profile of THV PVE was similar to surgical PVE, though one-quarter had satellite mitral valve endocarditis, and surgical intervention was required in 40%. Structural valve failure occurred most frequently due to leaflet calcification and was predominantly treated by redo-THV. Transcatheter heart valve thrombosis occurred at a mean  $9\pm 7$  months post-implantation and was successfully treated by prolonged anticoagulation in most cases. No thromboembolic events were attributed to THV thrombosis. Two novel causes of THV failure were identified: late THV embolization and THV compression following cardiopulmonary resuscitation. These failure modes have not been reported in the surgical literature. Potential risk factors for late THV embolization include low prosthesis implantation, THV undersizing/underexpansion, bicuspid, and non-calcified anatomy. Transcatheter heart valve embolization mandated surgery in 80% of patients. Transcatheter heart valve compression was noted at post-mortem in most cases. Late embolization and THV compression represent complications previously unreported in the surgical literature. Of course, this study is has limitations inherent to all systematic reviews, and the included studies were either case reports or small series, precluding comparison with the entire TAVI population at risk. Accurate estimation of the true incident rates of each THV failure mode was therefore not possible, and the likely underreporting of adverse events would be expected to result in a significant underestimation of event rates. Nevertheless, the identification and description of failure modes, and moreover the account of management strategies of these events provides both a reference for physicians and a foundation on which further studies can build.

## PART V. TRANSCATHETER MITRAL VALVE IMPLANTATION

One of the aims of this thesis was to draw on experience gained in the TAVI field to explore some basic principles of transcatheter mitral valve implantation (TMVI). As the prevalence of mitral valve disease is almost three times that of aortic valve disease,<sup>25</sup> this technique offers the potential to treat a great number of elderly and/or high-risk patients with severe mitral regurgitation (MR). Indeed, the Euro Heart Survey suggested that half of all patients hospitalised with symptomatic severe MR do not undergo potentially curative surgical repair/replacement due to advanced age, comorbid illnesses, and left ventricular dysfunction.<sup>11, 26</sup> There remains a great deal to learn about which patients could benefit from TMVI. Dr Elliot C. Cutler performed the first surgical mitral valve repair in 1939, yet the mode of repair/replacement and the timing of the intervention still remain topics of some debate. As with TAVI, patient selection is determined by anatomical and clinical criteria. Both involve complex decision matrices which require much clarification. Anatomically, TMVI is a veritable minefield: a large, non-circular, saddle-shaped, highly dynamic, non-calcified annulus without the ability for radial anchoring which is tethered to a complex, highly individualised, subvalvular

apparatus, and intimately related to the left ventricular outflow tract (LVOT), the coronary sinus, and the left circumflex coronary artery. Detailed MSCT analysis will be imperative for patient selection and preoperative procedural planning as this novel technology emerges in the next decade.

In **Chapter 17**, we describe recent developments in TVMI technology, outlining the design principles, construction, and available evidence for TMVI devices in early phase clinical trials. To date, five transcatheter mitral valve systems have been implanted in humans: CardiAQ valve system (CardiAQ Valve Technologies, Inc.); Tiara™ valve (Neovasc Inc., Richmond, Canada); FORTIS valve (Edwards Lifesciences, Irvine, CA, USA); Tendyne valve (Tendyne Inc., Roseville, MN, USA); and Twelve valve (Twelve, Inc., Redwood City, CA, USA). These devices share common features: nitinol self-expanding frames, trileaflet valves, bovine pericardial leaflets (Tendyne is porcine), fabric sealing skirt (CardiAQ is pericardial), and transapical delivery (CardiAQ also transseptal). Each of these systems, and those in preclinical development (Medtronic Mitral15 [Medtronic, Minneapolis MN, USA]; HighLife [HighLife Inc., Paris, France]), offer innovative design solutions to overcome the challenging anatomy of the mitral valve complex. TMVI systems must be flexible to deal with the complex and variable anatomy, provide large effective orifice areas, and deal with high transvalvular gradients. They must anchor without reliance on radial force (axial sealing), accommodate significant dislodgement forces, and avoid LVOT obstruction. Given these obstacles, additional areas of concern include stent fatigue and fracture, valve thrombosis, embolization, leaflet durability, and paravalvular leak with resultant haemolysis.

In the final chapters of this thesis (**Chapters 18 and 19**), we describe and evaluate a systematic MSCT image analysis methodology that provides measurements relevant for TMVI. A systematic step-by-step measurement methodology using a dedicated software package (3mensio Structural Heart 6.1 [Pie Medical Imaging BV, Maastricht, The Netherlands]) is described for structures of the mitral valvular complex including: the mitral valve annulus, left ventricle, left atrium, papillary muscles, and left ventricular outflow tract. This information is of relevance for those involved in the design and development of these novel transcatheter devices, and will be of importance in determining patient suitability in the future. Previous literature on mitral valve MSCT focused on establishing diagnosis and characterizing pathological states. Furthermore, the measurement methodology and nomenclature are heterogeneous among different authors. The systematic methodology presented here has the potential to facilitate the comparison of studies and the communication of results.

We applied this methodology to the MSCT data collected from a cohort of patients with severe functional mitral regurgitation recruited for the PTOLEMY-2 (NCT00787293) and PTOLEMY2Canada (NCT00815386) clinical trials of the Viacor percutaneous transvenous mitral annuloplasty system (Viacor, Inc., Wilmington, MA, USA). Herein, two independent observers measured 25 different geometrical properties of the mitral valve apparatus using the above-described methodology. The inter-observer difference (<10%) and the intra-class

correlation suggested excellent inter-observer agreement for most measurements. Among the patient population studied (N=32), the mean mitral annulus intercommissural and aorto-mural diameters were, respectively,  $41.5 \pm 5.2$  mm and  $38.7 \pm 5.9$  mm in systole. The obstacle-free zone below the mitral annulus averaged more than 20.0 mm and varied by less than 1 mm between systole and diastole.

These data have implications for the design of transcatheter mitral valves. The demonstration that, in patients with FMR, the mitral annulus is nearly symmetrical between its two major axes and contracts <2% in systole may alleviate concerns regarding excessive stress on the prosthetic valve frame. However, left ventricle immediately below the mitral annulus is highly dynamic and may substantially stress a device. The frame of a transcatheter valve may protrude on either aspect of the mitral annulus. In particular, the papillary muscles can represent an obstacle to the deployment of a transcatheter device. Our data however, demonstrates that the projected distance between the mitral plane and the heads of papillary muscles (the axial obstacle-free zone for the prosthesis) is approximately 20 mm and is constant during the cardiac cycle.

## CONCLUSIONS

The past decade has seen a revolution in the management of valvular heart disease, and in particular severe aortic stenosis. The emergence of transcatheter heart valve technology has the potential to change forever the way we treat patients with valvular heart disease. The appropriate selection of patients for TAVI by a multidisciplinary institutional heart team is of utmost importance for the individual patient, and indeed for the future of the therapy itself. In this thesis, we have provided important information on the anatomic, 3-D imaging, and clinical criteria used for patient selection.

TAVI technology continues to evolve at an astonishing pace and is being applied in new and innovative ways to treat patients. Application of this therapy to those with failing aortic and mitral bioprostheses and bicuspid aortic valve morphology represent important technical milestones. Continued scientific rigor is however required to ensure comparative efficacy with alternate treatment modalities. This is of particular relevance as the management of valvular heart disease will have an increasing impact on public health and health care resource consumption as the global population ages. Physicians, medical societies, and other stakeholders have a responsibility to ensure the appropriate use and sensible dispersion of this innovative technology.

The extension of TAVI technology to younger and lower-risk patient populations is imminent. This paradigm shift will be evidence-based with clear demonstration of transcatheter valve safety and durability in these patient groups.

Transcatheter mitral valve implantation has the potential to greatly impact patient care. The success of this technology will depend on innovative valve design, rigorous patient selection, and rigorous clinical evidence.

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